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Time and Extent Application (TEA) Review for Florastor (*S. boulardii*)

Division of Over-The-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research • Food and Drug Administration
Rockville • MD 20857

CONDITION	*Saccharomyces boulardii*, 250 mg (4.5×10^9 lyophilized, viable yeast cells), as an active ingredient taken 1-2 times daily with a maximum daily dose of 500 mg
PHARMACOLOGICAL CLASS	Antidiarrheal
MONOGRAPH	Antidiarrheal Drug Products (21 CFR Part 335)
APPLICANT	Parexel International The Quays, 101 - 105 Oxford Road Uxbridge, Middlesex UB8, 1LZ United Kingdom
SUBMISSION DATE	January 14, 2004
RECEIVED DATE	January 15, 2004
REVIEW DATE	January 22, 2004
REVIEWER	Michael L. Koenig, Ph.D.
TEAM LEADER	Matthew R. Holman, Ph.D.

BACKGROUND

The applicant requests addition of *Saccharomyces boulardii* (*S. boulardii*) as an active ingredient in the monograph for OTC antidiarrheal drug products (21 CFR part 335). This request follows a teleconference, in November 2002, between the following parties:

- representatives of Parexel International (the applicant)
- representatives of Laboratoires BIOCODEX (manufacturer of the finished product, Florastor)
- members of the Division of Over-the-Counter Drug Products (DOTCDP).

Parexel requested the teleconference to obtain guidance on the feasibility of submitting a TEA for Florastor (*S. boulardii*) as a treatment for symptomatic diarrhea.

REVIEWER'S COMMENTS

The nonpathogenic yeast *S. boulardii* is a botanical drug substance. The strain is registered in the American Type Culture Collection (74012), the French Institut Pasteur de Paris (I.7415), and the Netherlands Centraalbureau voor Schimmelcultures (CBS 5926). A detailed description of the lyophilized yeast product is presented in the application (section 1.2). Additionally, analytical test methods to verify viability, determine water content, and assess microbial contamination are provided in the application (section 1.3). *S. boulardii* is not listed in the United States Pharmacopeia-National Formulary (USP-NF). If the condition is found to be eligible, the applicant must include an official or proposed USP-NF monograph when data to validate safety and effectiveness are submitted, in accordance with 21 CFR 330.14(i). A final OTC drug monograph can only contain active ingredients recognized in official USP-NF drug monographs.

The applicant indicates that *S. boulardii* is marketed as an ingredient in antidiarrheal products in 64 countries worldwide (Table 1). Of these countries, the applicant selected 13 countries to serve as the basis of the TEA. *S. boulardii* has been marketed for more than 5 continuous years in each of these countries. Selected countries are identified by bold typeface in Table 1.

TABLE 1. List of all countries (64) in which *S. boulardii*-containing products have been marketed for the treatment and/or prophylaxis of diarrhea.[1]

Albania	Gabon	Myanmar
Argentina	Georgia	Niger
Armenia	**Germany**	Ouzbekistan
Azerbaidjan	Greece	Pakistan
Belgium	Guatemala	Paraguay
Benin	Guinea	Poland
Bielorussia	Hong Kong	**Portugal**
Bolivia	**India**	Romania
Burkina Faso	**Italy**	Russia
Brazil	**Ivory Coast**	**Senegal**
Bulgaria	Kazakhstan	**South Africa**
Cambodia	Kirghizistan	**Spain**
Cameroon	**Korea**	Sweden
Chile	Latvia	**Switzerland**
Columbia	Lithuania	Togo
Congo	Luxemburg	Tunisia
Cyprus	Madagascar	Turkey
Denmark	Mali	Ukrainia
Ecuador	Malta	Venezuela
Estonia	Mauritania	Vietnam
Finland	Mexico	
France	**Morocco**	

[1]Selected country shown in bold typeface.

The applicant states that *S. boulardii* "has been marketed in compliance with national legislation that is *equivalent* to OTC availability" (italics added for emphasis). *S. boulardii* is distributed only in pharmacies in 11 of the 13 selected countries, but the applicant has established that this marketing restriction is not due to safety concerns about the product. In Europe, S. boulardii is

available "with or without prescription." The applicant states that if there were concerns about the safety of *S. boulardii* as an "OTC (direct purchase and consumption without physician involvement)" drug product, it would have been classified in the "drugs on prescription only" category. The applicant asserts that in three African countries and India (which restrict sales of the product to pharmacies) the personal involvement of a pharmacist is not required. *S. boulardii* is available outside of pharmacies in two countries:

- South Africa - general stores
- Switzerland - drogeries (according to the applicant, these are analogous to U.S. drug stores with both pharmacy and cosmetics sales)

The total number of dosage units sold OTC in the selected countries was calculated by subtracting "prescription only" sales from "global" (total) sales and dividing that number by total sales. Based on total sales figures and the estimated percentage of sales attributable to "OTC" sales, the applicant estimates that a total of 1.16 billion dosage units were sold "OTC" in the selected countries over the 11 year period from 1993 through 2003 (Table 2). The combined population demographics of the 13 selected countries on three continents adequately reflects the racial and ethnic diversity of the United States.

TABLE 2. Estimated regional OTC sales of *S. boulardii* for the treatment of symptomatic diarrhea

Region	**Estimated total sales (million dosage units)**
Africa (4 countries)	40
Asia (2 countries)	17
Europe (7 countries)	1,103
Total (13 countries)	**1,160**

In accordance with 21 CFR 330.14(c)(2)(iv), the applicant lists differences in the patterns of use of *S. boulardii*. The applicant points out that, although there are differences in the selected countries, the drug is typically taken twice a day and daily doses are typically in the range of 250 to 500 mg, as the applicant proposes for U.S. dosing. According to the application, different

patterns of use in the selected countries are attributed to differences in "licensing decisions" made by independent national regulatory authorities.

The applicant does not report any adverse drug experiences (ADEs) in the selected countries. Although Ivory Coast and Senegal have no official organization for collecting and disseminating information about ADEs, 11 countries maintain systems for identifying ADEs similar to that maintained in the U.S. for drugs sold under a new drug application (NDA). The applicant also notes that *S. boulardii* has not been withdrawn from the market in any country.

Original and translated versions of the packaging are provided for each of the selected countries. The provided labeling includes directions and warnings information similar or identical to what is required on OTC antidiarrheal drugs marketed in the U.S. In addition, the application indicates that the provided labeling was approved by the appropriate regulatory bodies except in Ivory Coast, Senegal, and Morocco where, according to the application, labeling is not approved by a regulatory body.

S. boulardii is only available by prescription in the Scandinavian countries (i.e., Finland, Denmark, and Sweden) because it has been registered there for additional indications (other than symptomatic diarrhea):

(1) treatment of antibiotic-associated diarrhea

(2) treatment of recurrent intestinal infections due to *Clostridium difficile* in addition to standard antibiotic therapy

The drug is also restricted to prescription use in Turkey and Lithuania, but the applicant states that the sale of *S. boulardii* in Turkey is "equivalent to OTC [sale] irrespective of the indication."

RECOMMENDATION

I recommend that *S. boulardii*, at a maximum daily dose of 500 mg, be considered eligible for inclusion in the OTC antidiarrheal monograph. The condition is generally and widely available without prescription and has been marketed globally without reported safety concerns to a material extent and for a material time.